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TITLE: Improving the Specificity of High Resolution Breast MRI by  
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Models

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13. ABSTRACT (Maximum 200 Words)  Magnetic resonance imaging (MRI) techniques have the potential to greatly improve breast cancer detection, diagnosis, and treatment. The purpose of this study was to develop new diagnostic criteria for improved characterization of breast tissue using MRI. A high-resolution, three time-point, contrast-enhanced MR technique was optimized for image quality, breast coverage, and time efficiency, and over 200 patients were imaged prior to undergoing surgery. Several models incorporating the dynamic enhancement response of the breast tissue were proposed and the diagnostic value of each was tested against pathology results. One of the best performing models was the signal enhancement ratio (SER), which compared early to late enhancement behavior in the tissue. SER values successfully differentiated between benign and malignant tissue ( $p < 0.05$ ), and showed promising results for quantifying tumor aggressiveness. Additionally, the diagnostic value of diffusion-weighted MRI of the breast was investigated. Diffusion-weighted images were acquired using a newly developed technique, and apparent diffusion coefficients (ADC) were calculated in the breast tissue of volunteers. Mean ADC values were found to be significantly different ( $p < 0.01$ ) for tumor, normal tissue and cysts measured in the breast. The optimized models are now being evaluated for detecting neoadjuvant treatment response in breast tumors, and may be capable of detecting changes much earlier than current clinical methods.				
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## INTRODUCTION

Breast cancer is the most common malignancy of women in the United States, and is the second leading cause of cancer death in American women. Contrast-enhanced breast MRI has shown greater sensitivity than mammography in the detection of small breast lesions, detecting tumors at sizes less than 1cm, and can also successfully image the dense breast (1-5). Additionally, MRI is a valuable tool in surgical planning for lumpectomy, can be used for monitoring tumor response to therapy, and has demonstrated usefulness in distinguishing scar tissue from recurrent breast carcinoma (6-8). New models which accurately describe tissue characteristics such as tumor grade, size, histologic type, extent of angiogenesis or microvessel density, etc. using breast MRI would be valuable predictive tools in the diagnosis and treatment of breast cancer (9).

The purpose of this study is to develop and optimize new diagnostic models for improved differentiation between benign and malignant breast tissue and enable accurate characterization of tumor extent and aggressiveness of breast cancer using MRI. It is hypothesized that the addition of dynamic enhancement data from muscle and vessels to models which currently utilize only lesion enhancement information will improve tumor differentiation and will minimize patient to patient variations to improve the overall specificity of MRI in the detection of breast cancer. Breast MRI data acquisition techniques will be modified and patient data will be analyzed to provide optimal dynamic behavior information of the tissues. The performance of the resulting models will be evaluated and the increase in MRI specificity due to the application of optimized models will be quantified. This research will contribute to the overall development of a high resolution 3D imaging method for staging of breast cancer and monitoring treatment response, and ultimately facilitate the transition of breast MRI from a research tool to a clinically useful technique.

## BODY

### Technical Objective 1: Development of MRI Data Acquisition Techniques

**MRI Acquisition Sequences.** The contrast-enhanced MRI data acquisition sequence was formalized corresponding to our temporal and spatial resolution requirements. We worked to maximize the temporal resolution of the data acquired for increased dynamic enhancement information of the tissues while still maintaining high spatial resolution to adequately identify tumor extent. While we originally expected to reduce our scan time considerably, we found that this was not feasible with current limitations. We have requirements on our contrast-enhanced imaging sequence which include full breast coverage, fat suppression, and high spatial resolution. Working with these restraints and our current hardware limitations, we were able to reduce our scan time from 5.6 minutes to 5.0 minutes per acquisition without sacrificing image quality.

Additionally, a new diffusion-weighted MR sequence was investigated for usefulness in identifying breast cancer. MRI non-invasively measures the apparent diffusion coefficient (ADC) of water, which is sensitive to the biophysical characteristics of tissue. Previous work has shown that ADC values in the brain are significantly different for tumor and normal tissue (10), and significant differences ( $p < 0.01$ ) were found between the ADC values for malignant masses, benign masses, and cysts in the liver (11). Diffusion-weighted imaging of breast cancer tumors implanted in mice has been successful at differentiating viable tumor cells from necrosis and fibrosis, and detecting early treatment response within tumors (12-14). A recent study was able to obtain reproducible measurements of diffusion coefficients of breast tissue in vivo in human volunteers using diffusion-weighted MRI (15). Preliminary findings from this group also demonstrate differences in the ADC values for normal breast tissue, cancer, and cysts, indicating the potential for using diffusion imaging to improve the specificity of breast MR and for classifying breast lesions. Additional advantages of diffusion imaging are the short scan times, taking less than a minute per scan, and the fact that no contrast injection is needed for this type of imaging.

We developed a diffusion-weighted single-shot fast spin echo sequence for use in the breast and it was incorporated into the breast MR exams following the contrast-enhanced acquisitions. Imaging parameters included TE/TR = 86ms/8s, 35cm field of view, 5mm slice thickness, a b-value of 578 s/mm<sup>2</sup>, and a scan time of 32s. Diffusion-weighted images were obtained both in normal volunteers and those with breast tumors, and studies were conducted to determine the value which diffusion measurements provide to diagnostic models for characterizing breast cancer.

In a group of normal volunteers, we assessed the variation in ADC values measured in the breast due to hormonal fluctuations during the menstrual cycle. Results showed a significant influence of menstrual cycle on breast ADC values ( $p = .028$ ). There was a trend of decreased ADC during the second week of the cycle, and increased ADC during the final week, with significant differences between the mean ADC values for the 2<sup>nd</sup> and 4<sup>th</sup> weeks. The average change in ADC between the 2<sup>nd</sup> and 4<sup>th</sup> weeks was 7.8%. The results of this study suggest that breast diffusion measurements for tumor differentiation and evaluation of treatment response should be interpreted with

consideration of normal variability. It may also be important to schedule serial DWI exams for a woman during the same menstrual phase for consistency of measurements. *See appended abstract for more details on the diffusion MRI studies in the breast.*

Although it was originally proposed that preliminary testing on animals would be an efficient method for developing new acquisition sequences, we have not found this to be true. Many logistical problems have made it difficult to directly translate from imaging animals to humans on our clinical scanner. These issues include the small size of the animals necessitating use of a different receiver coil, faster heart and breathing rates affecting image quality and enhancement rates, and difficulty of achieving controlled contrast injections in the mice. In conclusion, we feel that the ample number of human volunteers available at our center renders the animal studies unnecessary for this work.

**Analysis Software.** The MR images are evaluated on a Sun Ultra 1/170E workstation (Sun Microsystems, Mountain View, CA). All image analysis software was created with IDL (Interactive Data Language, Research Systems, Boulder, CO). Many new functions have been incorporated into the previously developed analysis software. To accommodate different scanning techniques, the software was adapted to allow measurements to be taken from more than three time points. The software now allows the user to manually register images from any of the multiple time points to adjust for patient motion between acquisitions. The user can draw an ROI on one time point, and measurements will automatically be taken from corresponding locations in all time points. This data can be recorded by writing to a file for further analysis or can be displayed on a plot in order to view changes with time.

In addition, new methods were developed for taking accurate measurements in vessels. It was found that the relatively small size of most vessels in the breast makes it difficult to draw an ROI contained within a vessel, and also that most vessels are virtually invisible on our precontrast T1-weighted images, making it difficult to obtain a reliable precontrast vessel measurement. The new technique requires the user to draw an ROI on the vessel of interest on the post-contrast maximum intensity projection (MIP), where the projection of the vessel is much larger than it would be in a single sagittal image. The software then uses the pixels from the same locations for taking ROI measurements from the precontrast and other postcontrast scans.

Another exciting area of development with the software is the addition of a semiautomated volumetric analysis algorithm. Current major problems associated with breast MRI are the large amount of image data, the time-intensive analysis required, and varying reproducibility of measurements (16,17). By automating the technique, we feel the analysis of patient exams can be performed in a more timely and reproducible manner, and thus improve the clinical utility of breast MRI. Total analysis time for a patient study was reduced from 30-45 minutes for the manual analysis to approximately 5 minutes using the new semiautomated technique (18). This new method is designed to gather the same measurements from breast MRI studies which are currently collected manually, and in addition allows many new volumetric quantifications to be made to better characterize the lesions. We feel these MRI measurements may provide a powerful quantitative method to non-invasively measure changes in tumor volume and biologic activity over the course of treatment.

Studies have been completed to compare the performance of the new semiautomated analysis technique to the manual method and to investigate the value of the volumetric measurements for identifying treatment response in tumors (19). Results showed that measurements obtained with the semiautomated analysis could be used to diagnose equally as well as those obtained with the manual method, with a large time-savings and improved reproducibility. The improved efficiency of analysis will aid further development and testing of new models for characterizing breast lesions. Additionally, in serial MR exams in a group of women undergoing neoadjuvant chemotherapy treatment, changes in volumetric measurements were assessed for identifying treatment response in tumors. A significantly greater volume response was observed during neoadjuvant treatment in the women who, following neoadjuvant therapy and surgery, showed no signs of recurrence than for the group of women with metastasis or recurrence at 18 month follow-up. *See appended abstracts for more details of the automated software and clinical application for monitoring treatment response.*

**Patient Database.** A spreadsheet was initially created using Microsoft Excel (Microsoft Corporation, Redmond, WA) to organize patient data for developing diagnostic models. Information contained in the spreadsheet included measurements at each time point from enhancing lesions, vessels, and muscle, and pathology diagnosis of the lesions for each patient. Eventually this data was incorporated into a larger database containing all patient data, compiled from treatment, clinical, surgical and histological assessments, as well as MR. The larger database was developed using a FileMaker Pro (FileMaker, Inc., Santa Clara, CA), and statistical analysis of particular parameters is currently done using Excel spreadsheets with data downloaded from the larger database.

## **Technical Objective 2: Optimization of MRI diagnostic specificity**

**Patient MR Exams.** Many patient exams have been processed using the new software to measure enhancement in lesion, muscle, and vessels and all measurements and calculations are recorded in the patient database. All appropriate older studies stored on optical disks were analyzed, and new studies have been systematically processed after each patient is scanned. Patients included in the study are those who are imaged prior to undergoing surgery. Subsequent pathology reports are used as the gold standard for comparison with MRI results. MR exams for over 200 patients were analyzed by completion of this study.

**Diagnostic Models.** The main goal of this study was to develop diagnostic models to accurately characterize breast tissue, based on MRI enhancement kinetics in comparison with results from pathology. After sufficient patient data was collected, diagnostic models were investigated to improve the specificity of our contrast-enhanced imaging technique. Five models were proposed to characterize enhancing regions of breast MRI images, incorporating measurements from breast lesions, blood vessels, and normal muscle tissue during the three time points. It was hypothesized that the addition of enhancement data from muscle and vessels to the models would improve tumor differentiation and reduce inconsistencies between patients due to variances in delivery of



contrast agent and differences in circulation of contrast in the body. Two of the models tested incorporated muscle and vessel information.

Investigations were then made to ascertain the best performing models for differentiating between types of breast lesions. Thresholds and cutoffs for calculations were further optimized to minimize the effects of noise and to improve discrimination between benign and malignant tissue. ROC curve analysis was used to assess the diagnostic value of each of the proposed models based on proven patient diagnosis as determined by pathology. Further, the significance of the discrimination between different pathologies (DCIS and different tumor grades) was evaluated by the Student-Newman-Keuls test for multiple comparisons.

One of the best performing models for separating benign from malignant was a signal enhancement ratio (SER). SER compares early to late enhancement behavior in the tissue and is calculated by  $(S1-S0)/(S2-S0)$ , where  $S0$ ,  $S1$  and  $S2$  are the pre-contrast, 2.5min, and 7.5min post-contrast tissue measurements, respectively. SER showed statistically significant results ( $p<.05$ ) for differentiating between benign and malignant lesions, with benign lesions tending to have lower SER values and average SER increasing with tumor grade. This response is believed to be a function of tumor vascularization. It was determined that an  $SER > 1.0$  combined with an overall enhancement of at least 80% produced the highest diagnostic specificity of 79% with a sensitivity of 94% (20). While the SER indexes show strong differences between benign and malignant tissue, they only marginally discriminate between the types and grades of tumors. Other models evaluated demonstrated statistically significant differences between the grades of tumor and DCIS. A model of SER/PE where PE is the percent enhancement of the first post contrast image successfully differentiated between high grade tumors and all other pathologies including benign, DCIS and lower grade malignancies. This is a potentially important discrimination for treatment planning. In addition, a model of relative washout of the contrast in the tissue calculated by  $(S1-S2)/S0$  was able to differentiate between moderate grade malignancies and high grade comedo-type DCIS and also between low grade non-comedo DCIS and benign tissue to a significance of  $p<.05$ . Attempts of using muscle and vessel signal changes to normalize enhancement curves did not significantly improved specificity in these analyses (21). Additionally, it has been suggested that for patients who have recently completed chemotherapy, MR contrast enhancement rates and levels are affected and may necessitate a different set of criteria for evaluation(22). In future work, we will assess this problem.

In addition, apparent diffusion coefficient maps were generated from the new DW-MRI acquisitions. Measurements were taken from normal tissue and in breast tumors, and statistical analysis was used to determine the potential of DW-MRI for identifying and characterizing tumors in the breast (23). In a group of 13 women with breast cancer, significant differences were found for ADC values of tumor, normal breast tissue, and cysts (with mean ADC values of  $1.01 \pm 0.19$ ,  $1.53 \pm 0.31$ , and  $2.27 \pm 0.37 \times 10^{-3} \text{mm}^2/\text{s}$ , respectively). These values correlate well with those reported by the other groups, and further work will investigate the use of diffusion-weighted imaging for assessing treatment response in breast tumors treated with chemotherapy.



*See appended abstracts for more details of the development and validation of diagnostic criteria for differentiating tumor and benign tissue using both contrast-enhanced and diffusion-weighted MRI.*

## KEY RESEARCH ACCOMPLISHMENTS

- Formalized contrast-enhanced MR acquisition sequence and collected measurements from over 200 patient MR exams for development and testing of diagnostic models.
- Developed a new semiautomated software technique to increase the efficiency of analysis of breast MR exams and to help characterize volumetric parameters as well as dynamic response of breast lesions.
- Proposed and tested models incorporating dynamic enhancement data in lesions and assessed the effect of normalizing models with measurements from corresponding vessels and muscles. Using ROC analysis, determined the optimal models for differentiating benign from malignant breast tissue.
- Developed new breast diffusion-weighted MRI protocol and tested the performance in normal volunteers and patients with breast lesions. Initial measurements showed significant differences in diffusion measurements between tumor, cyst, and normal tissue in the breast. In addition, a slight dependence was found of breast ADC on phase of the menstrual cycle.

## REPORTABLE OUTCOMES

### ***Publications:***

1. Partridge S, Esserman L, Kaplan E, Heumann E, Weidner N, Hylton N. Method for quantitative assessment of tumor volume response to neoadjuvant chemotherapy using MRI. Proceedings of the World Congress on Medical Physics and Biomedical Engineering, Chicago 2000.
2. Partridge S, McKinnon G, Newitt D, Day M, Hylton N. Influence of menstrual phase on apparent diffusion coefficients measured in the breast. Proceedings of the ISMRM 8<sup>th</sup> Scientific Meeting, April 2000; 492.
3. Partridge S, Heumann E, Hylton N. Semi-automated analysis for MRI of breast tumors. Studies in Health Technology and Informatics, 1999; 62:259-60.
4. Partridge S, Esserman L, Heumann E, Tripathy D, Hylton N. Validation of a semi-automated breast MRI analysis technique for tumor diagnosis and evaluation of response to therapy. Proceedings of the ISMRM 7<sup>th</sup> Scientific Meeting, May 1999; 3:2170.
5. Hylton NM, Esserman LJ, Partridge SC, et al. Clinical Evaluation of a three-time point breast MRI method. Proceedings of ISMRM 6<sup>th</sup> Scientific Meeting, April 1998; 2:933.
6. Partridge SC, Hylton NM, Wang WL. A comparison of analytical models for improved discrimination of benign and malignant breast tissue. Proceedings of ISMRM 6<sup>th</sup> Scientific Meeting, April 1998; 2:934.

### ***Manuscripts in Submission:***

Partridge SC, McKinnon GC, Henry RG, Hylton NM. Menstrual cycle variation of apparent diffusion coefficients measured in the normal breast using MRI. Journal of Magnetic Resonance Imaging.

### ***Academic Degree Supported by this Award:***

PhD, Bioengineering

University of California, Berkeley/University of California, San Francisco

Expected Graduation Date: March 2001

## CONCLUSIONS

We have completed the tasks outlined in the approved Statement of Work for this grant, as well as additional related investigations. A versatile software tool was developed for enabling all necessary measurements to be taken from the patient studies. In addition, a semiautomated algorithm was incorporated into the software to increase the efficiency of analysis and to help characterize volumetric parameters as well as dynamic response of breast lesions. Data from contrast-enhanced scans was used to develop and validate diagnostic models for improved discrimination of breast lesions. Diffusion-weighted MRI has the potential to provide valuable insight to biologic activity in the tissue of the breast. A new protocol was developed for acquiring diffusion-weighted images of the breast, and initial results are promising for characterizing breast tissue, and may ultimately improve diagnostic models.

I intend to complete the final stages of this project within the next few months, leading to my PhD in Bioengineering. During this time, I will focus more on using the results of the diagnostic models developed for assessing treatment response for neoadjuvant chemotherapy. A combination of contrast-enhanced and diffusion-weighted MRI may provide a powerful quantitative method to non-invasively measure changes in tumor volume and biologic activity over the course of treatment. This will depend on the development of analytical methods that are accurate, efficient, and not subject to operator variability. Such a methodology could greatly aid in the evaluation of new treatment strategies in clinical trials by offering a more accurate method of assessing tumor response than is currently available using mammography, ultrasound, and clinical exam.

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## **Final Report**

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### **PERSONNEL**

- Savannah Partridge, the PI, is the only person who received salary support from this research grant (Grant #17-98-1-8191).



## **APPENDICES**

# Method for Quantitative Assessment of Tumor Volume Response to Neoadjuvant Chemotherapy Using MRI

Savannah Partridge<sup>1</sup>, Laura Esserman<sup>2</sup>, Elizabeth Kaplan<sup>2</sup>, Emily Heumann<sup>3</sup>,  
Noel Weidner<sup>4</sup>, Nola Hylton<sup>3</sup>

**Abstract** – Neoadjuvant chemotherapy is an effective treatment for locally advanced breast cancer (LABC). Response of a tumor to preoperative chemotherapy is a valuable predictor of a patient's overall survival. We hypothesize that magnetic resonance imaging (MRI) may be more predictive of patient outcome than clinical exam by providing quantitative assessments of extent of cancer in the breast and the change in response to neoadjuvant treatment. The purpose of this study was to investigate whether MRI can accurately quantify changes in tumor size in response to treatment.

MRI size measurements were compared to clinical response assessments and post-surgical pathology data in a group of women with LABC. The MR techniques accurately characterized size of residual disease in the breast and demonstrated predictive value for treatment outcome.

**Key words** – Magnetic resonance imaging, breast tumors, neoadjuvant chemotherapy, treatment response, tumor volume, image segmentation

## I. INTRODUCTION

Neoadjuvant or preoperative chemotherapy for locally advanced breast cancer (LABC) is increasingly being used to shrink large tumors to make them operable and enable patients to receive breast-conserving surgery. It has been shown that a tumor's response to pre-operative chemotherapy, characterized as a change in size detected by clinical exam, is a valuable prognostic indicator of a patient's overall survival<sup>i</sup>. Furthermore, pathologic response to chemotherapy as determined by size of residual disease has been shown to be the best predictor of patient outcome<sup>ii</sup>. Identifying surrogates which can predict pathologic response to therapy would be valuable for tailoring treatments to individual patients. It is also important to identify those patients who are unlikely to respond to treatment so that a change in management may be introduced at an earlier time, sparing them from additional ineffective and toxic treatment. Magnetic resonance imaging (MRI) techniques have the potential to improve breast cancer

detection, diagnosis, and treatment. MRI has been shown to be superior to mammography and clinical exam in demonstrating tumor extent in the breast and may prove more effective than clinical exam at identifying treatment response<sup>iii-iv</sup>. The purpose of this study was to investigate whether MRI can accurately detect changes in tumor size in response to treatment.

## II. METHODS

A group of 34 women with LABC were imaged prior to starting 4 cycles of neoadjuvant adriamycin/cyclophosphamide (AC) chemotherapy and again at the completion of treatment and prior to surgery. 18 of these patients also had an MRI exam following the first cycle of chemotherapy. A high-resolution, 3D, fat-suppressed MR acquisition was used in each exam. Three time points were acquired, a baseline scan before contrast injection ( $t_0=0$ ), followed by two sequential post contrast scans ( $t_1=2.5$  minutes and  $t_2=7.5$  minutes after contrast injection).

Tissue contrast enhancement was assessed quantitatively by measuring the percent enhancement,  $PE=(S_1-S_0)/S_0$ , and signal enhancement ratio,  $SER=(S_1-S_0)/(S_2-S_0)$ , where  $S_0$ ,  $S_1$ , and  $S_2$  are the 0, 2.5 and 7.5 minute signal intensities. The PE measure quantifies the overall level of enhancement, and the SER index compares early to late enhancement behavior in the tissue. While some benign lesions may demonstrate significant enhancement, it has been observed that they typically have lower SER values than malignant lesions. This response is believed to be a function of tumor vascularization. ROC curves were used to optimize cutoffs of PE and SER values to produce diagnostic models which most accurately differentiate between benign and malignant tissue in the images. Use of the resulting models produced a diagnostic sensitivity of 94% with a specificity of 79% for detecting breast cancer in a test group of 157 women with suspicious lesions<sup>v</sup>.

A semi-automated software tool was created to compute tumor volumes from patient MR exams by applying the developed diagnostic models<sup>vi</sup>. The software algorithm first creates a set of maximum intensity projections (MIPs) from the images at each time point. The projections are made in the

latero-medial, cranio-caudal and antero-posterior directions, and allow the tumor extent to be quickly identified in all dimensions. The optimized enhancement criteria using PE and SER indices was applied by the software to segment the tumors in the 3D MR datasets and calculate tumor volumes. Figure 1 demonstrates a sagittal post-contrast MR image from a dynamic series with a corresponding SER map.

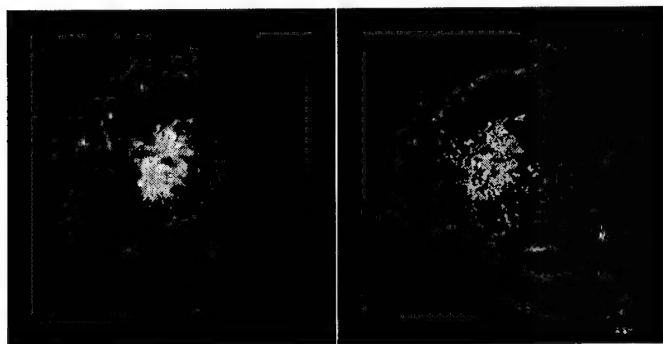


FIGURE 1. Left image is a post-contrast sagittal 2D image. Image on the right is the corresponding SER map used by automated software algorithm to segment the tumor for volume calculations. SER index values are represented in descending order by red (highest values), green, and blue (lowest values) in the colormap.

The longest diameter (LD) for each tumor was also measured on the MIPs for correlation with pathology tumor size assessments. Figure 2 shows post-contrast MIPs with a longest diameter measurement displayed on the cranio-caudal MIP. The tumor in this example is easily identified as the brightly enhanced area of breast tissue. Large enhanced vessels are also visible. Darker areas in the breast correspond to non-enhanced (normal) breast tissue regions of suppressed fat signal in the MRI images.

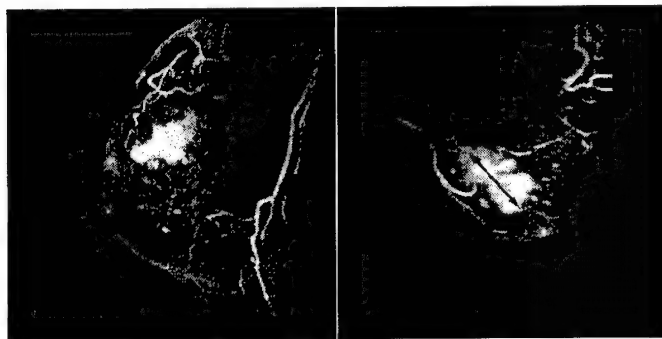


FIGURE 2. Examples of post-contrast maximum intensity projections created in the latero-medial (left image) and cranio-caudal (right image) directions. Red line indicates the LD on the cranio-caudal view.

Clinical response was determined as a palpable change in tumor size upon examination by a clinician. After surgical excision of the tumors by mastectomy or lumpectomy, the size (LD) of residual disease was assessed by pathology. The measurements from pathology were used as the gold standard for size information on the tumor. However, it can often be

difficult to determine the exact size of larger tumors due to the nature of pathology sampling in mastectomy specimens. Changes in tumor size measured with MRI, both volume and longest diameter, were compared to clinical response assessments and also correlated with post-surgical residual pathology data.

### III. RESULTS

An excellent correlation ( $r = 0.89$ ) was demonstrated between the tumor size detected by MRI in post-chemo exams and actual tumor size determined from pathology after surgical excision. Figure 3 shows a scatterplot of these results and corresponding linear regression line.

#### Size of Residual Disease: MRI vs. Pathology

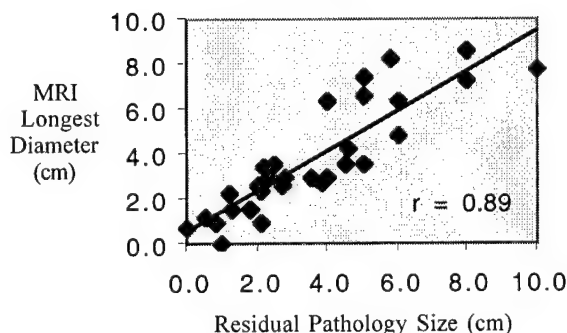


FIGURE 3. Scatterplot displaying lesion size measured with MR and the true size as determined by pathology observation. There is a strong correlation between the two measurements ( $r=0.89$ ), indicating that MR can accurately identify residual tumor.

The changes measured in tumor volume after completion of treatment correlate very well with change in LD as measured by MR ( $r=0.91$ ). The same comparison was made for the subset of MR exams acquired mid-treatment, comparing size before and after the first cycle of chemotherapy. In this case, the correlation between change in size by volume and size by LD was less strong ( $r=0.66$ ). We have observed in certain types of tumors such as lobular carcinomas, a tendency for the tumor to recede in a diffuse manner such that while tumor volume changes substantially, the tumor continues to extend over a large area. This may be responsible for the weaker correlation of LD and volume changes at the mid-treatment time point.

In addition to measuring size of response, we are also able to quantify the pattern of response (diffuse or focal shrinking of the tumor) and are interested to investigate whether the response pattern or changes in the tumor SER distribution are predictive of outcome. Figure 4 displays post-contrast MIPs generated before and after undergoing neoadjuvant treatment in a patient with good response.

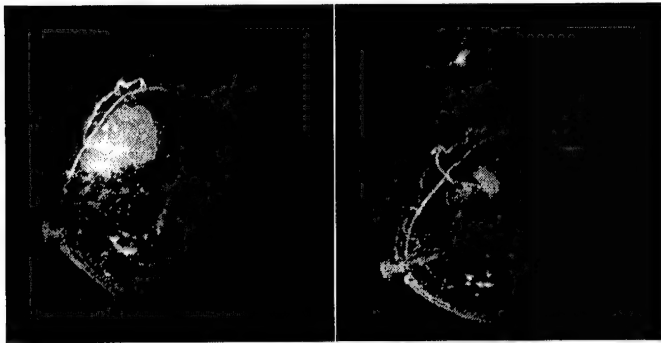


FIGURE 4. Latero-medial MIPs for a patient prior to neoadjuvant treatment (left) and after completion of chemotherapy treatment (right). The change in tumor size in this case demonstrates good response to the neoadjuvant treatment.

Comparison of MR volume response and clinical response assessments produced only a weak correlation ( $r=0.31$ ). This result was not surprising and may suggest that MR methods are more accurate for identifying treatment response and ultimately may better predict patient outcome than clinical exam alone.

#### IV. DISCUSSION

The results of this study indicate that MR methodology could greatly aid in the evaluation of new treatment strategies in clinical trials by offering a more accurate method of assessing tumor response than is currently available. In addition, MR measurements provide new variables such as tumor shrinkage pattern and change in tumor SER distribution to study as indicators for treatment response and predictors of treatment success. Size of residual disease following therapy has been identified as the best predictor of patient outcome. In this study, the MR measures of residual tumor size following chemotherapy correlated strongly with post-surgical pathology determinations of size. These results illustrate the strong potential of MR for use as a surrogate to predict pathologic response, and ultimately facilitate future improvements in management of patients with breast cancer.

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# Influence of Menstrual Phase on Apparent Diffusion Coefficients Measured in the Breast

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## Introduction

Recent studies have successfully distinguished differences in the apparent diffusion coefficient (ADC) values of breast tumors, cysts, and benign breast tissue [1,2]. Diffusion-weighted imaging (DWI) may prove useful for characterization of breast disease and may be a sensitive measurement of response to therapy [3]. Our goal for this study was to assess the influence of hormonal fluctuations on the variability in measured ADC values in the breast, and also to characterize the ADCs of tumors, cysts, and uninvolved breast tissue of women with breast cancer.

## Methods

Imaging was done on a 1.5T GE Signa scanner using a bilateral phased array breast coil. A T1-weighted SE sequence was first acquired to provide more detailed anatomical information for post-processing purposes. Diffusion data was acquired using a diffusion-weighted single-shot FSE (DW-SSFSE) pulse sequence based on the technique described by Alsop [4]. This sequence was chosen to minimize image distortion due to magnetic susceptibilities. All images were acquired axially with FOV=35x35cm, thickness=5mm, 128x128 matrix, b=0 and 600 s/mm<sup>2</sup>. DW images were acquired in the x, y, and z directions independently. ADC maps were generated using the technique described by Horsfield, et al [5].

**Group 1:** 6 volunteers who had regular, 28-day menstrual cycles and were not taking oral contraception were imaged. The ages ranged from 22-34yrs (mean =27yrs) and all were nulliparous. All volunteers were scanned once a week for 4 weeks to assess cyclic variations. Region of interest (ROI) measurements of the ADC maps were taken in the same locations within the breast for each woman at each of the 4 time points. Menstruation dates reported by the volunteers were used to determine the phase of the menstrual cycle for each scan, with week 1 beginning on the first day of menstruation.

**Group 2:** 12 patients with invasive breast cancer were scanned prior to undergoing surgery. In these women, contrast-enhanced, T1-weighted 3DFGRE images obtained prior to diffusion imaging were used to accurately identify the lesion locations. Mean ADCs were measured for tumor, uninvolved benign tissue (defined as non-contrast-enhancing parenchyma on T1-weighted images), and cysts in the patient scans.

## Results

**Group 1:** The mean ADCs and standard deviations (SD) were calculated for the women at each time point. The inter-subject variability ( $SD=0.23 \times 10^{-3} \text{ mm}^2/\text{s}$ ) was found to be greater than the intra-subject variation in ADC (for the same woman over time, mean  $SD=0.10 \times 10^{-3} \text{ mm}^2/\text{s}$ ). The overall means for the group did not change significantly with menstrual phase, indicating there is minimal effect of menstrual cycle on ADC values measured in the normal breast. Results are shown in Figure 1.

**Group 2:** There were significant differences ( $p<0.01$ ) found by t-test between the mean ADCs found for tumor, uninvolved benign tissue, and cysts ( $0.97 \pm 0.19$ ,  $1.47 \pm 0.31$ , and  $2.19 \pm 0.37 \times 10^{-3} \text{ mm}^2/\text{s}$ , respectively). A water phantom included for reference in the imaging was measured to have  $ADC=2.060 \pm 0.27 \times 10^{-3} \text{ mm}^2/\text{s}$  at a temperature of approx. 20°C. This is lower than the ADC found for cyst due to the higher temperature of the cysts. Additionally, the mean ADC found for benign tissue in patients agrees well with the mean ADC found in normal volunteers ( $1.60 \pm 0.18 \times 10^{-3} \text{ mm}^2/\text{s}$ ) even though the groups were not age-matched. Results are shown in Figure 2.

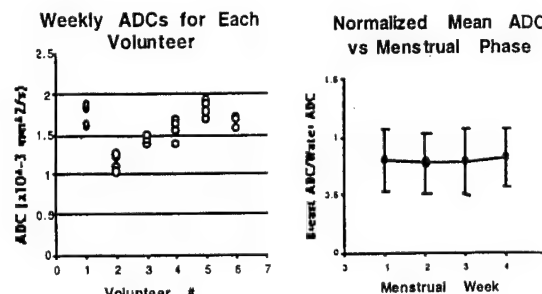


Figure 1. The charts above illustrate the variation found in the breast ADCs of the women through the course of their menstrual cycles. Chart on the left shows the 4 ADC measurements from each week of the cycle plotted for each volunteer. Chart on the right displays the mean ADC for the group at each phase of the menstrual cycle normalized to the ADC of a water phantom imaged with the volunteers each time.

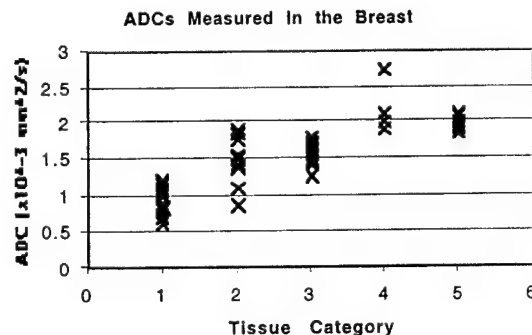


Figure 2. ADC values are plotted for each tissue category. Categories are 1=tumor, 2=benign tissue in patients, 3=normal tissue in volunteers, 4=cysts, 5=water phantom.

## Discussion

In our study of changes with menstrual phase, we found that although the mean ADC values for different women can vary widely, little variation was seen for each woman throughout her cycle. Additionally, significant differences were demonstrated between the mean ADCs for tumor, benign tissue, and cysts in the breast. The variability between tumor ADCs was greater than that which could be explained by hormonal fluctuations, indicating the potential for using diffusion to characterize tumor type. The tumors in this study were all invasive, but continuing studies will evaluate discrimination of DCIS and other pathologies as well as changes which occur with neoadjuvant treatment.

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# Semi-Automated Analysis for MRI of Breast Tumors

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Magnetic resonance imaging (MRI) techniques have the potential to greatly improve breast cancer detection, diagnosis, and treatment. Currently, a major problem associated with breast MRI is the overwhelming amount of data acquired during an exam, and the time-intensive analysis required to evaluate the images. We have developed a software platform for semi-automated analysis to assess both the tumor extent and overall grade or severity based on our diagnostic criteria. In a test subset of over 50 patients, the automated program produced results more accurate overall than those measurements taken manually, with a reduction in time for analysis from approximately 45 minutes down to 5 minutes per patient study.

## **1. Introduction and Purpose**

Breast cancer is the most common malignancy and the second leading cause of cancer death among American women. Although mammography is currently the most common detection method, contrast-enhanced breast MRI has shown greater sensitivity than mammography in the detection of small breast lesions, and can also successfully image dense, augmented, and postoperative breasts.[1,2] Additionally, MRI is becoming a valuable tool in surgical planning for lumpectomy and can be used for monitoring tumor response to therapy.[3]

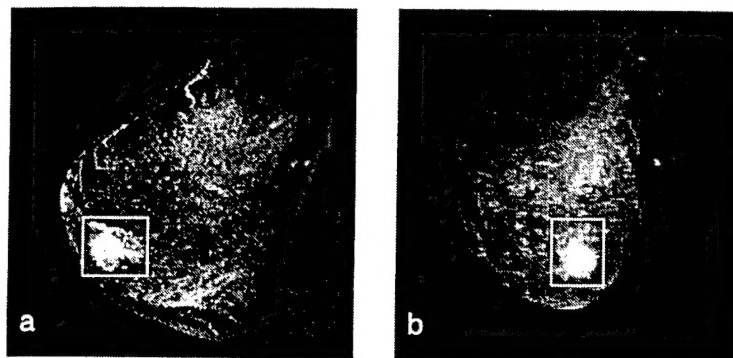
Diagnostic techniques for breast MRI involve assessing both the morphology and the pattern of contrast enhancement kinetics; a number of recent publications have proposed diagnostic models incorporating these features.[4,5] Due to the large amount of data acquired, these diagnostic assessments are time-intensive and typically take more than 30 minutes to evaluate a single breast MRI exam. In addition, a skilled operator must perform the analysis and interoperator variability may affect the reproducibility of the results.

The purpose of this study was to design a semi-automated method for evaluation of breast MRI exams which would produce a diagnostic assessment including lesion extent, diagnosis, and tumor characterization. By automating the technique, analysis of patient exams can potentially be performed in a more timely and reproducible manner.

## **2. Methods**

The MR images are evaluated on a Sun Ultra 1/170E workstation (Sun Microsystems, Mountain View, CA). The analysis software platform was developed using the Interactive Data Language (IDL, Research Systems, Boulder, CO) programming environment. The diagnostic model we currently use at our institution is the signal enhancement ratio (SER) index for suspicious enhancing lesions which compares early to late enhancement behavior in the tissue and has shown promising results for quantifying tumor aggressiveness and differentiating between benign and malignant lesions. [6]

The manual analysis technique requires the user to browse through the images of corresponding locations at different times after injection to take measurements and determine lesion extent. The user searches for the highest SER value in the lesion by manually drawing regions of interest (ROIs) for which signal intensities and SERs are calculated. The new semi-automated technique reduces the number of images a user must view by first generating maximum intensity projections (MIPs) in three orthogonal directions from the



**Figure 1.** MIPs of MR images of the entire breast acquired 3 minutes post-contrast injection. a) Latero-medial, and b) Cranio-caudal with user-defined boxes indicating volume to be evaluated.

data for each time point. This condenses the information from 180 images to a set of 9 images, which allows the user to more quickly evaluate the extent of the lesion. (Figure 1) Next, the user draws a box around the lesion (Figure 1b) on two orthogonal projections, defining a restricted volume to be evaluated. The software calculates SER values for all voxels within the defined volume and identifies the peak SER as the ROI (>5 contiguous voxels) with the highest mean SER value. Tumor volume is then calculated by summing voxels within the region which meet tumor enhancement criteria. The pattern of enhancement is also characterized by identifying the proportion of voxels with high, moderate or low SER values.

### 3. Results and Conclusions

Fifty-seven patients with suspicious mammographic or clinical findings were scanned prior to undergoing surgery. The diagnostic results of benign or malignant from the analysis using both techniques were compared to histopathology reports. The pathologies included 13 benign and 44 malignant (including 8 non-invasive malignancies) cases. The semi-automated analysis was equally as accurate as the manual technique, with both methods correctly diagnosing 48 cases in 57 and achieving sensitivities of 93% and specificities of 57%. A reduction in time for analysis was observed from approximately 45 minutes for the manual method to 5 minutes for the semi-automated method. While reproducibility studies have not yet been performed, our feeling is that the reproducibility is much higher for the semi-automated technique since the only interaction by the user is to define the boundaries of the restricted volume in order to include the entire lesion.

The new semi-automated technique allows analysis to be done more quickly and with less training for accurate and potentially more reproducible results. This improvement in efficiency will ultimately facilitate the transition of breast MRI from a research tool to a clinically useful technique.

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# Validation of a Semi-Automated Breast MRI Analysis Technique for Tumor Diagnosis and Evaluation of Response to Therapy

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## Purpose

The purpose of this study was to validate a semi-automated method for lesion diagnosis and evaluation of lesion extent and enhancement kinetics.

## Introduction

Contrast-MRI may provide a powerful quantitative method to non-invasively measure changes in tumor volume and biologic activity over the course of treatment, but this will depend on the development of analytical methods that are accurate, efficient, and not subject to operator variability. Such a methodology could greatly aid in the evaluation of new treatment strategies in clinical trials by offering a more accurate method of assessing tumor response than is currently available using mammography, ultrasound, and clinical exam.

Current major problems associated with breast MRI are the large amount of image data, the time-intensive analysis required, and varying reproducibility of measurements.[1,2] By automating the technique, analysis of patient exams can potentially be performed in a more timely and reproducible manner and thus improve the clinical utility of breast MRI.

## Methods

56 patients with suspicious mammographic or clinical findings were imaged prior to undergoing surgery. Subsequent pathology reports for each patient were compiled and information on lesion grade, size, and histologic type (benign, ductal carcinoma in situ (DCIS), invasive, etc.) were recorded for comparison with the results of manual and semi-automated image analyses.

All patients were imaged using a fat-suppressed 3D-FGRE sequence, TR/TE=11.2/4.2ms, 2 NEX, 18cm FOV, sixty 2mm thick slices, 256x192 matrix, on a 1.5 T GE Signa Echospeed imager using a dedicated breast receiver. Three imaging sequences were acquired, one before contrast injection (Time 0) and two consecutively after (Time 1 and Time 2, centered around 2.8 minutes and 8.1 minutes respectively after injection of 0.1mmol/kg body-weight Gd-DTPA).

All image analysis software was created with IDL (Interactive Data Language, Research Systems, Boulder, CO). Manual MR image analysis consisted of defining regions of interest (ROIs) inside suspected lesions for which average signal intensities are then calculated at each time point (S0, S1, S2). The diagnostic model used is the signal enhancement ratio (SER) index for suspicious enhancing lesions which compares early to late enhancement behavior in the tissue and is calculated by  $(S1-S0)/(S2-S0)$ . SERs have previously shown promising results for quantifying tumor aggressiveness and differentiating between benign and malignant lesions. [3] The user found the highest SER value by choosing ROIs at various locations in the lesion, and determined lesion extent by measuring it at its widest points.

In the semi-automated technique, the user defines a restricted volume by drawing a box around the lesion on two orthogonal maximum intensity projection (MIP) views created from the Time 1 images. (Fig. 1) The software calculates SER values for all voxels within the defined volume with enhancement >80% and identifies the peak SER as the ROI (>5 contiguous voxels) with the highest mean SER value. Tumor volume is then calculated by summing all voxels with appropriate SER (>1.0), and the pattern of enhancement is characterized by identifying the fraction of tumor with high, moderate or low SER values. The user is given

the opportunity to reject the initial automated ROI selection if it is found to be improperly chosen inside a vessel. This analysis method is limited by misregistration due to patient motion.

To investigate whether this method is useful in quantifying response to treatment, and in particular identifying early response, measurements were taken of 31 invasive lesions in 24 patients undergoing neoadjuvant chemotherapy. In addition to changes in tumor volume and peak SER value for the lesion, we also quantified changes in the fractions of the lesion with high and low SER values.

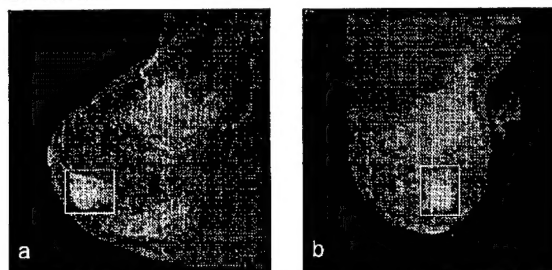


Figure 1. a) Latero-medial, and b) Cranio-caudal MIPs with user-defined boxes indicating volume to be evaluated.

## Results

The diagnostic value of both analysis techniques was tested against proven patient diagnosis as determined by pathology. In a group of 56 lesions (consisting of 12 benign, 7 DCIS, and 37 invasive pathologies) evaluated, the semi-automated program produced results equally as accurate as measurements taken manually. Both analysis techniques independently produced sensitivities of 93% and specificities of 50%. (Note: This image analysis did not incorporate morphologic features which have been shown to increase diagnostic specificity. [4]) An overall reduction in time for the quantitative analysis was observed from approximately 45 minutes down to 5 minutes per patient study using the semi-automated technique, with a marked observed improvement in the reproducibility of the measurements.

In the group of patients receiving neoadjuvant chemotherapy, we found that changes in tumor volume correlated well with clinical and pathologic assessment of tumor response. The significance of SER changes over the course of treatment has not yet been established, however in continuing studies we are investigating whether SER response in combination with volumetric response is predictive of patient outcome.

## Discussion

The new semi-automated technique allows analysis to be done more quickly and with less training for accurate and potentially more reproducible results. This improvement in efficiency will ultimately facilitate the transition of breast MRI from a research tool to a clinically useful technique.

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## Acknowledgments

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# Clinical Evaluation of a Three-Time Point Breast MRI Method

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## Introduction

MRI is proving to be effective as an adjunct procedure to mammography for evaluation of the symptomatic breast. We present the results of a clinical evaluation of 203 patients using a high resolution 3D imaging and analysis method.

## Methods

Our interest in using breast MRI for pre-operative staging motivated the development of a high resolution, fat-suppressed 3D method to demonstrate the extent of disease in a single symptomatic breast. To better characterize tumor heterogeneity and increase the specificity of this method, we used a second post-contrast scan to evaluate contrast washout. Contrast enhancement was characterized using the signal enhancement ratio (SER) which compares enhancement behavior at two key points in the uptake curve; near the peak and at a delayed time point when fibroglandular tissue has enhanced significantly and some washout has occurred.

203 patients were enrolled over the period between February 1994 and November 1997. Subject age ranged from 27 to 76 years with an average age of 50 years. The subject population consisted primarily of women with a confirmed diagnosis of breast cancer on the basis of fine needle aspiration (FNA), core or surgical biopsy, or failed excision (n=111). A subset of women were evaluated for diagnostic purposes and included women with mammographic or clinical abnormalities recommended for biopsy (n=61). Other reasons for referral included patients with axillary metastasis and an unknown primary (n=7), suspicion of recurrence (n=11), high risk screening (N=4), and follow-up of previous MR findings (n=20).

We previously described the triple acquisition rapid gradient echo technique (TARGET), which is a high resolution technique designed for local staging in symptomatic women<sup>1</sup>. TARGET consists of one precontrast ( $S_0$ ) and two post contrast ( $S_1$  and  $S_2$ ) acquisitions of a fat-suppressed 3D sequence; TR = 11 ms, TE = 4.2 ms, flip angle 20°, FOV = 16-20 cm, slice thickness = 1-2 mm, imaging matrix = 256x192, oversampling to remove phase wrap (2 NEX), scan time 5.4 minutes. Fat-suppression is accomplished using a spectrally-selective inversion recovery prepulse<sup>2</sup>. The temporal sampling was 0, 2.8 and 8.1 minutes. Image analysis was performed as follows: Breast tissue showing greater than 80 percent signal enhancement (PE) in the  $S_1$  image was considered suspicious for malignancy. Contrast enhancement was further analyzed in suspicious tissue by computing the signal enhancement ratio (SER) =  $(S_1 - S_0) / (S_2 - S_0)$ .

Diagnostic specificity was calculated based on a 2x2 table using a criteria of PE > 80% as the condition for MR malignancy and pathologic diagnosis as the gold

standard. This was compared to the diagnostic specificity using the combined criteria: PE > 80% and SER > 1.2.

## Results

Pathology results were available for 157 patients. Pathology findings were unavailable for 46 patients and include those who underwent neoadjuvant chemotherapy, have not yet had surgery or who chose to have surgery elsewhere. Of the 157 patients with pathology, 54 had benign findings and 103 had malignant findings. When PE > 80% was used as the sole criteria for malignancy, we found diagnostic sensitivity and specificity to be 98% and 36%, respectively. By increasing this criteria to PE > 90%, specificity increased to 46% with a decrease in sensitivity to 94%. When we used the combined criteria, PE > 80% and SER > 1.2, we found sensitivity and specificity values of 94% and 79%, respectively.

## Discussion

By reducing the temporal sampling to only three appropriately chosen time points, scan time constraints can be relaxed and high resolution imaging can be used to demonstrate heterogeneity in both tumor anatomy and enhancement behavior. The three time points used in the TARGET technique were a consequence of the timing of successive 5.4 minute data acquisitions and were not optimized for specificity. Degani et. al. also proposed a three-time point method and found optimal time points to be 0, 3.5 and 12 minutes using a dose of 0.08 mmol/kg Gd-DTPA, in mouse models and human breast carcinoma<sup>3</sup>. TARGET, or a similar three-point 3D imaging method, can be easily implemented on most commercial scanners. The SER index provides a simple way to quantify and convey the enhancement behavior of tumors, leading to greater specificity.

## Conclusions

The additional signal intensity information provided by a second post-contrast data acquisition, can substantially improve the specificity of a 'static' high resolution breast MRI method. Using a criteria of SER > 1.2 to identify high likelihood of malignancy, we realized a 33% improvement in specificity, with equals or exceeds values reported using dynamic techniques, without a loss of sensitivity. A three-time point method such as TARGET, combines the high specificity of dynamic techniques with the sensitivity of high resolution imaging and offers complete breast evaluation in a single exam.

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# A Comparison of Analytical Models for Improved Discrimination of Benign and Malignant Breast Tissue

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## Introduction:

Breast MRI techniques have the potential to greatly improve breast cancer detection, diagnosis, and treatment. Our imaging technique was designed primarily for presurgical staging of disease extent and therefore a priority was placed on achieving high resolution images with relatively low temporal resolution. In order to improve specificity, we acquired an additional post contrast time point. The purpose of this study was to investigate analytic models for improved differentiation between benign and malignant breast tissue and enable accurate characterization of tumor extent and aggressiveness using contrast-enhanced breast MRI.

## Methods:

The majority of our patient population have confirmed malignancies as determined by biopsy or fine needle aspiration (FNA). Over one hundred patients were imaged prior to undergoing a surgical procedure. All patients were imaged using a fat-suppressed 3D-FGRE sequence, TR=11.2ms, TE=4.2ms, 2 NEX, 18-20cm FOV, 256x192 matrix, on a 1.5 T GE Signa Echosped imager using dedicated breast coils, resulting in 60 2mm thick sections with in-plane resolution of 0.6-0.8mm and scan time of 5.4 minutes. Three imaging sequences were acquired, one before contrast injection (Time 0) and two consecutively after (Time 1 and Time 2, centered around 2.8 minutes and 8.1 minutes after contrast injection, respectively). Using a software tool developed with IDL (Interactive Data Language) to analyze the images, regions of interest (ROIs) were defined inside vessels, chest muscle, and suspected lesions. Average signal intensities were calculated for these regions at each time point (S0, S1, S2 for lesions, M0, M1, and M2 for muscle, and V0, V1, and V2 for vessels). Figure 1 illustrates a typical ROI defined for an enhancing lesion and corresponding images obtained at each time point. Registration problems resulting from patient motion between the three scans was minimized using interactive registration tools incorporated in the software. Pathology reports from biopsy, FNA, or surgery for each patient were compiled and information on the lesion grade, size, and histologic type (benign, ductal carcinoma in situ (DCIS), invasive, etc.) were recorded for evaluation of the models. Several models incorporating the dynamic enhancement response of the breast tissue were evaluated for their ability to better discriminate between different pathologies.

## Results:

The diagnostic value of each of the proposed models was tested against proven patient diagnosis as determined by pathology. The significance of the discrimination was evaluated by the Student-Newman-Keuls test for multiple comparisons. It was hypothesized that the addition of enhancement data from muscle and vessels to the models would improve tumor differentiation and reduce inconsistencies between patients due to variances in delivery of contrast agent and differences in circulation of contrast in the body. Two models incorporating muscle and vessel information were tested. One of the best performing models for separating benign from malignant was a signal enhancement ratio (SER), which compares early to late enhancement behavior in the tissue and is calculated by  $(S1-S0)/(S2-S0)$ . SERs showed statistically significant results ( $p<.05$ ) for differentiating between benign and malignant lesions. Benign lesions tend to have lower SERs, with average

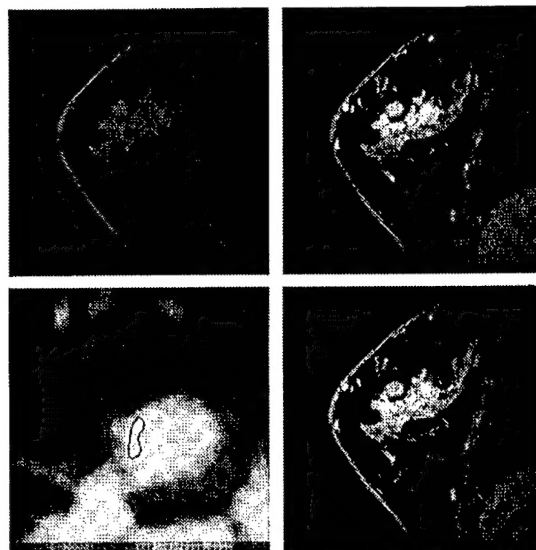


Figure 1. Clockwise from upper left: Time 0 sagittal image of breast, before contrast is injected (S0), Time 1 image at 2.8 minutes after injection (S1), and Time 2 image 8.1 minutes after injection (S2), typical ROI as defined in lesion on Time 1 image (zoom factor of 8).

SERs increasing with tumor grade. This response is believed to be a function of tumor vascularization. While the SER indexes show strong differences between benign and malignant tissue, they only marginally discriminate between the types and grades of tumors. Other models evaluated demonstrated statistically significant differences between the different grades of tumor and DCIS. A model of SER/PE where PE is the percent enhancement of the Time 1 post contrast image successfully differentiated between high grade tumors and all other pathologies including benign, DCIS and lower grade malignancies. This is a potentially important discrimination for treatment planning. In addition a model of relative washout of the contrast in the tissue calculated by  $(S1-S2)/S0$  was able to further differentiate between moderate grade malignancies and high grade comedo-type DCIS and also between low grade non-comedo DCIS and benign tissue to a significance of  $p<.05$ . Initial investigations of using muscle and vessel signal changes to normalize enhancement curves, using models such as did not significantly improve specificity in these analysis.

## Conclusions:

SERs showed promising results for quantifying tumor aggressiveness and differentiating between benign and malignant lesions. Other models were able to better discriminate tumor grades than were SERs and even showed promise at differentiating benign from low grade DCIS and malignant from higher grade comedo-type DCIS. Future work will focus on exploring the addition of morphological information to the models, further testing of utilizing muscle and vessel information, and investigating differences between pathology classifications such as ductal, lobular, and various benign pathologies to better characterize the disease.

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